40. (New) The array of claim 34, wherein the modified oligonucleotide is further characterized by modification of at least 25% of the internucleoside linkages of the oligonucleotide.

41. (New) The array of claim 34, wherein said modified oligonucleotides have an average length of from about 80 to about 300 nucleotides.

42.(New) The array of claim 34, wherein said modified oligonucleotides have an average length of from about 100 to about 200 nucleotides.

43.(New) The array of claim 34, wherein oligonucleotides of each of said oligonucleotide compositions has a different sequence from oligonucleotides of any other oligonucleotide composition on the array.

44.(New) The array of claim 34, wherein each oligonucleotide composition comprises a population of identical oligonucleotides.

45.(New) The array of claim 34, wherein each oligonucleotide composition comprises a plurality of oligonucleotides that bind to a particular nucleic acid.

46.(New) The array of claim 34, wherein the number of oligonucleotide compositions on said array ranges from about 2 to about 10^9. –

REMARKS

Claims 34-46 are pending in this application.

Claims 22-33 have been canceled, and claims 34-46 added, to more particularly point out and distinctly claim the invention. Support for new independent claim 34 can be found in originally filed claim 1 and throughout the specification, particularly at page 11, lines 1-7; page 38, Example 2 (lines 1-17) and page 10, lines 2-26.

Support for dependent claims 35 and 36 can be found at page 8, lines 11-15.

Support for dependent claim 37 can be found at page 11, lines 4-6.

Support for dependent claims 38 and 39 can be found throughout the specification , with an exemplary passage at page 10, lines 17-18.

Support for dependent claims 40-46 can be found in originally filed claims 13 and 4-9, respectively.

No new matter is a added by any of the amendments.

Telephonic Interview with Examiner

Applicants are grateful for the recommendations of Examiner in the telephone conversation of 8/29/00, and such recommendations are incorporated herein to ensure responsiveness of the present application. The claims as amended herein are in the same group as the originally elected claims.

The Invention in General

The presently pending claims are directed to arrays with associated compositions of 1) oligonucleotides having increased acid stability and increased binding relative to a naturally occurring nucleic acid having the same sequence; 2) where such modified oligonucleotides are associated on a substrate and 3) where the oligonucleotides of the compositions are designed so that each oligonucleotide composition will have approximately the same T_m as the other compositions on the array when bound with the target nucleic acid. These arrays have numerous advantages over arrays known in the art. These characteristics also allow the clearance of the target nucleic acids from the arrays of the invention, allowing the arrays to be reused. Compositions having constant T_m can also allow for hybridization of target nucleic acids to the array at an optimized temperature for binding. Clearance of the target nucleic acids can also be optimized for a specific temperature.

The acid stability of the bound oligonucleotides allows the clearance of the target nucleic acids by subjecting the arrays to acidic conditions. In addition, the fact that each associated compositions is designed to have approximately the same T_m with its target binding partner allows the array to be

designed for use at a same specific stringency, *e.g.*, high stringency to ensure selective hybridization or low stringency to identify related molecules.

The oligonucleotides of each composition also may have an end block to enhance exonuclease stability. This provides an exonuclease stability to allow the array to be directly contacted with target nucleic acids from biological sources, *e.g.*, human tissue, without requiring purification to elminate the exonucleases present in the samples.

Restriction Requirement

In view of the restriction requirement, Applicants again confirm election of Group I, claims 1-15, directed to an array comprising a plurality of modified oligonucleotides. The remaining claims have been canceled in the previous Response to Office Action without prejudice to renewal as being directed to nonelected subject matter. The new claims added herein claim the subject matter of Group I, as they are directed to an array comprising a plurality of modified oligonucleotides having an increased binding affinity and an increased acid stability relative to naturally occurring oligonucleotides.

Objection to the Specification

The specification was objected to for failing to comply with 37 CFR 1.821 through 1.825. This objection has been rendered moot by the amendment to the specification at page 38, which adds the SEQ ID NO to the disclosed sequence in the specification. This amendment was also stated in the previous Response to Office Action, and is repeated herein to ensure that this amendment is entered into the specification.

A sequence listing is also being filed herewith to comply with 37 CFR 1.821 through 1.825. As the specification discloses only two sequences, and the sequences themselves are not an inventive feature of the claimed arrays, the election of 10 sequences should not be needed to proceed with examination of the application.

Rejection of claims 1-9 and 15 under 35 USC §112, first paragraph

Claims 1-9 and 15 were rejected under §112, first paragraph for containing subject matter which was not described in the specification in a manner to allow one skilled in the art to practice the invention as described. This rejection is traversed as applied, and as it may be applied to the presently pending claims, but is also rendered moot by the new claims. Specifically, Examiner rejected the originally filed claims as requiring undue experimentation to determine the modifications that would result in increased binding affinity of the oligonucleotides of the array of the invention. The currently pending claims specifically recite that the associated compositions of the invention are all designed to have the same T_m with a specific target nucleic acid of interest. The design of oligonucleotides having the same T_m is sufficiently described in the specification to allow one skilled in the art to practice the invention as claimed without undue experimentation. Moreover, the 2' ribose modification and the end block are described at length, and would not require undue experimentation.

The acid stability of the molecules is experimentally demonstrated in the examples of the present application, as is determination of T_m for various binding pairs. Acid stability is described in Example 3 and 4, pages 38-40. Determination of T_m for various binding pairs is described in the specification at Example 2, page 38 lines 1-17.

Accordingly, Applicants respectfully request withdrawal of the §112, first paragraph rejection of originally filed claims 1-21 as it may be applied to presently pending claims 34-46.

Rejection under 35 USC §112, second paragraph

Claims 1-9 and 14-15 were also rejected under §112, second paragraph, for failing to particularly point out and distinctly claim that which is the subject matter of the invention. The rejection is traversed, but is rendered moot by the language of the presently pending claims.

Claim 34 claims an array having associated oligonucleotide compositions with 1) increased binding affinity as compared to a naturally occurring oligonucleotide of the same sequence; 2) increased acid stability relative to a naturally occurring oligonucleotide of the same sequence; 3) at least one nucleotide of the oligonucleotides of each composition having a 2' ribose substitution and 4) substantially the same T_m upon binding of the associated oligonucleotides with a target nucleic acid, be it RNA or

DNA. Thus, the metes and bounds of the modifications of the oligonucleotides are clearly stated. Claim 35, which claims associated compositions of oligonucleotides having end blocks, now specifically recites that the an end block is at either the 5' or 3' end of the associated oligonucleotide.

Accordingly, Applicants respectfully request withdrawal of the §112, second paragraph rejections as they might apply to the presently pending claims.

Rejection of claims 1-9 and 14 under 35 USC §103(a)

Claims 1-9 and 14 stand rejected under §103 as obvious over U.S. Pat. No. 5,986,083 (hereafter "Dwyer") in view of WO 94/15619 (hereafter "Miller"), or over Dwyer and Miller in further view of U.S. Pat. No. 5,861,242 (hereafter "Chee"). These rejections are traversed as applied, and as they may be applied to the presently pending claims.

To establish a case of prima facie, three basic criteria must be met: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §§2143-2143.03. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991).

The presently pending claims are not prima facie obvious over the cited art, as the art does not meet all of the elements of prima facie obviousness. Specifically, the prior art does not teach each and every limitation of the invention as claimed, and thus one skilled in the art would not have had motivation to combine all of the elements of the present invention.

Dwyer et al. are cited as describing modified oligonucleotides which exhibit nuclease stability and an enhanced binding affinity with complementary target nucleic acids. Dwyer et al. do not, however, describe 1) oligonucleotides having increased acid stability; 2)oligonucleotides having an increased binding as compared to naturally occurring nucleic acids; 3) oligonucleotides of the compositions designed so that each oligonucleotide composition will have substantially the same T_m as the other compositions on the array with the target nucleic acid; and 4) oligonucleotides having all of these

characteristics associated on a substrate. Dwyer et al also does not specifically describe oligonucleotides having an end block to enhance exonuclease stability of the oligonucleotide.

Miller et al. is cited as describing an oligonucleotide having a 2' modification to a 2'-O-alkyl. Although this is demonstrated in Miller to confer acid stability onto the molecule, Miller does not describe molecules associated on an array, associated compositions having approximately the same T_m for the intended nucleic acid targets, or an end block to enhance exonuclease stability.

Finally, Chee et al., which is cited as describing a high density array of oligonucleotides immobilized on a solid support, does not teach oligonucleotides having enhanced acid stability, enhanced binding ability, enhanced nuclease stability, and associated compositions having approximately the same T_m for the intended nucleic acid targets.

Accordingly, as each and every limitation is not taught nor suggested by the references alone or in combination, the claims are not *prima facie* obvious over the cited art. The references do not teach or suggestion the claimed combination, and thus one skilled in the art would not be motivated to combine the elements of the present invention to obtain an array with the beneficial properties of the present invention. Applicants respectfully request withdrawal of the §103(a) rejection and allowance of the claims as presently pending.

Conclusion

The presently pending claims have been amended or added to more distinctly claim the subject matter of the invention. The invention is sufficiently described in the specification to allow one skilled in the art to practice the invention as claimed. Moreover, the claimed invention is not obvious over the cited art, as the art does not teach each and every element of the claimed invention and the combination would not prompt one skilled in the art to conceive of or practice the present invention. Accordingly, Applicants respectfully request allowance of the claims as pending.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 8/31/00

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